REMARKS

Claims 1-6, 13-16 and 49-51 are pending and under consideration in the instant application. With the instant Amendment, Claims 1, 49 and 50 are amended, and new Claims 52-54 are added. For the PTO's convenience, a clean copy of pending Claims 1-16 and 49-54 are attached hereto as Exhibit B.

I. THE AMENDMENT TO THE CLAIMS

With the instant Amendment, Claims 1, 49 and 50 have been amended, and new Claims 52-54 have been added.

Claims 1 and 49 have been amended merely to clarify the time period during which a pharmacologic agent is administered to the patient. Support for the amendments to Claims 1 and 49 can be found in the specification, for example, at page 4, lines 20-21, and at page 8, lines 18-20. Claim 49 has also been amended to correct a minor error in claim language. Support for the amendment to Claim 49 can be found in the specification at, for example, page 13, line 16, through page 14, line 12. Finally, Claim 50 has amended to correct a minor error in claim language. Support for the amendment to Claim 50 can be found in the specification at, for example, page 11, line 28, through page 12, line 2.

New Claims 52-54 are fully supported by the specification and claims as originally filed. For example, new Claims 52-54 are supported by original Claim 1 and by the specification, for example, at page 4, lines 20-21, at page 8, lines 18-20, and at page 5, lines 15-17.

As the amendments to Claims 1, 49 and 50 and new Claims 52-54 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Since the amendments do not constitute new matter and are believed to place the claims in condition for allowance, entry thereof is therefore respectfully requested.

II. THE REJECTION UNDER 35 U.S.C. § 112

Claim 49 stands rejected under 35 U.S.C. § 112, second paragraph. The PTO asserts that the term "and" in original Claim 49 should be amended formally to "or." Applicant has so amended Claim 49. Applicant submits that amended Claim 49 meets the requirements for

patentability under 35 U.S.C. § 112 and respectfully requests that the rejection of Claim 49 be withdrawn.

III. THE REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-6, 13-16 and 49-51 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Goldstein *et al.*, 1993, *J. Cardiovasc. Pharmacol.* 22:253-258 ("Goldstein"). The rejection is respectfully traversed on the ground that Goldstein is not sufficient to establish a *prima facie* case of obviousness against Claims 1-6, 13-16 and 49-51.

A. The Legal Standard of *Prima Facie* Obviousness

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992).

In order to establish *prima facie* obviousness, three basic criteria must be met. First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *See id.* The mere fact that references *could* be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art,

must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside* , 53 USPQ2d 1769 (Fed. Cir. 2000). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If *any one* of these criteria are not met, *prima facie* obviousness is not established, and Applicants are *not* required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

Even if *prima facie* obviousness is established, an applicant can rebut the *prima facie* showing of obviousness with arguments and/or evidence demonstrating the nonobviousness of the claimed invention. *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). A *prima facie* case of obviousness may be rebutted, for example, by showing that the claimed invention exhibits a superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected. *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). That which would have been surprising to a person of ordinary skill in an art would not have been obvious.

B. Goldstein Fails to Render Claims 1-6, 13-16 and 49-51 *Prima Facie* Obvious

As discussed in section A, above, in order to render Claims 1-6, 13-16, and 49-51 *prima facie* obvious, Goldstein must teach or suggest each and every element of those claims. Each and every element of Claims 1-6, 13-16, and 49-51 are not taught or suggested by Goldstein. Claim 1, and Claims 2-6, 13-16, and 50-51 which depend therefrom, recite methods for reducing cardiovascular disease complications in a patient following surgery comprising the step of administering to the patient a pharmacologic cardiovascular agent near the maximum effective dose of the agent while certain conditions are met in the period that begins *prior to, during or immediately after surgery* and continues daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital. Independent Claim 49 recites a similar method for reducing

cardiovascular disease complications in a patient following surgery comprising the step of administering to the patient a pharmacologic cardiovascular agent near the maximum effective dose of the agent while certain conditions are met in the period that begins *prior to, during or immediately after surgery* and continues daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital. Goldstein does not teach or suggest each and every element of Claims 1-6, 13-16, and 49-51.

In particular, Goldstein does not teach administration of a pharmacologic cardiovascular agent to a patient in the period *prior to, during or immediately after surgery* until symptoms of cardiovascular stress are reduced or the patient is discharged. Instead, Goldstein teaches waiting until two full hours following extubation before the administration of atenolol.

The methods of instant Claims 1-6, 13-16, and 49-51 are based on Applicant's startling discovery that the administration of a pharmacologic cardiovascular agent to a patient in the period during surgery or immediately following surgery significantly reduces mortality and serious cardiovascular complications following surgery and discharge. In fact, such administration improves long term survival of surgical patients for two years or longer. While not intending to be bound by any theory of operation, it is believed that the effects of the administration are the result of the pharmacologic cardiovascular agent reducing the the patient's cardiovascular stress in the period following surgery.

Following surgery, a patient can experience multiple stress responses including, for instance, increases in heart rate, increases in blood pressure, myocardial ischemia and atherosclerotic plaque instability. For example, many stress responses are associated with the abrupt withdrawal of the anaesthetic given during surgery. During anesthesia, the anesthetic protects the heart and other organs by creating an anaesthetic state in which responses to severe surgical stimuli such as cutting through ribs, abdomen and other organs, are blunted. Following closure of the skin, anesthetic concentrations are typically reduced to allow the patient to emerge, wake up and assume mental and physical function. Within 15 minutes of reducing the anesthetic, patient reflexes typically return and the patient attempts to assimilate environmental change, emergence from an anesthetic state, responses to severe pain and trauma induced during surgery, and changes in respiratory function, temperature regulation and hormonal function. The responses from surgical trauma can be severe and at the limits of

human experience. When measured by hemodynamic and hormonal indices, such responses exceed even those of the most strenuous exercises.

Excitotoxic stresses can cause profound and persistent elevations in heart rate, elevationsin blood pressure, myocardial ischemia, heart failure, myocardial infarcation and even cardiac death. Furthermore, one-third or more of patients undergoing surgery are at high risk of having atherosclerotic plaques in arteries supplying major organs, and these plaques tend to clot as a result of the inflammatory stresses associated with surgery.

The manifestation of such stress responses is a poor indicator for the long-term survival of a patient. For instance, post-operative development of a heart attack during hospitalization increases the risk of death by 200 % over the next two years. Development of myocardial ischemia during the first 48 hours following surgery increases the risk of developing a heart attack during hospitalization by 900 %. See, *e.g.*, Mangano *et al.*, 1990, *N Engl J Med* 323:1781-8; Hollenberg *et al.*, 1992, *JAMA* 268:205-9; Eisenberg *et al.*, 1992, *JAMA* 268:210-16; O' Kelly *et al.*, 1992, *JAMA* 268:217-221; Browner *et al.*, 1992, *JAMA* 268:228-32; Mangano *et al.*, 1992, *JAMA* 268:233-39. Applicant discovered that a patient's long-term survival improves when the patient is protected from stress responses during the immediate post-operative period.

Accordingly, the methods of instant Claims 1-6, 13-16, and 49-51 recite administration of the pharmacologic cardiovascular agent in the period prior to, during or immediately following surgery and continuing daily thereafter protect the patient from stresses discusses above that could result in elevation of blood pressure, myocardial ischemia, heart failure, myocardial infarction and/or cardiac death.

Goldstein, on the other hand, fails to teach any administration of a pharmacologic cardiovascular agent in the period prior to, during surgery or immediately following surgery and continuing daily thereafter. Goldstein teaches no administration at all in the critical period immediately following surgery through extubation. Furthermore, Goldstein fails to teach any administration of an agent for two full hours following extubation. The patient experiences multiple stresses during these period as discussed above including, particularly, the withdrawal of anesthetic and the stress of extubation itself. The period between surgery and two hours following extubation can be as much as 24 hours or longer. Goldstein thus fails to teach or suggest administration of a pharmacologic cardiovascular agent in the period

prior to, during surgery or immediately following surgery as recited in instant Claims 1-6, 13-16, and 49-51.

Furthermore, because Goldstein administers an oral dose of atenolol, Goldstein's method is not sufficient to provide continuous protection of a patient with a pharmacologic cardiovascular agent as recited in instant Claims 1-6, 13-16, and 49-51. An oral dose of atenolol must be absorbed through the digestive system before the atenolol can possibly protect the patient from the stresses following surgery. In a healthy, ambulatory patient, peak blood levels of atenolol are not achieved until two to four hours following an oral dose (see, *e.g.*, Physician's Desk Reference, Medical Economics Company, Inc., 2001). In patients following surgery, absorption of an oral dose can take much longer due to poor digestive function and the effects of other medications such as narcotics. Thus, even when Goldstein finally provides the patient a dose of atenolol, the patient still receives no protection until at least four hours following extubation, and probably much longer.

Finally, Goldstein does not teach administration of a pharmacologic cardiovascular agent near its maximal dose. The PTO asserts that the could be a near maximum effective dose depending on the patient to which Goldstein administered the agent. The PTO speculates that depending on the age, weight and renal status of the patient, a 50 mg dose as taught by Goldstein might be a near maximum effective dose. However, Goldstein in fact does not teach a near maximum effective dose. Goldstein, provides the patient data for his method. According to Goldstein, patients with an average weight of 78 kg received a daily dose of 50 mg of atenolol. In contrast, a near maximum effective dose of atenolol is, on average, about 2 mg/kg (see, *e.g.*, Physician's Desk Reference, Medical Economics Company, Inc., 2001), and a near maximum effective dose for patients with an average weight of 78 kg is, on average, 156 mg. Goldstein's dose of atenolol is therefore less than one-third of the average maximum effective dose for Goldstein's patient population. Goldstein thus fails to teach or suggest administration of a pharmacologic cardiovascular agent near its maximum effective dose.

Since Goldstein fails to teach administration of a pharmacologic cardiovascular agent in the period prior to, during immediately following surgery and continuing daily thereafter near its maximum effective dose, Goldstein fails to teach or suggest each and every element of Claims 1-6, 13-16, and 49-51 and is not sufficient to render the claims *prima facie*

obvious. Applicant respectfully requests that the rejection of Claims 1-6, 13-16, and 49-51 under 35 U.S.C. § 103 be withdrawn. Applicant also submits that new Claims 52-54 meet the requirements for patentability under 35 U.S.C. § 103.

CONCLUSION

Applicant submits that Claims 1-6, 13-16 and 49-54 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-6, 13-16 and 49-54 to issuance is therefore kindly solicited.

No fees in addition to the appeal and extension fees are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds U.S. Deposit Account No. 16-1150.

Respectfully submitted,

Date: July 5, 2001

Rahul Pathak (Reg. No. 42,983)

For: Samuel B. Abrams (Reg. No. 30,605)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Exhibit A
Marked Up Copy of Amended Claims

1. (Three Times Amended) A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent [after surgery] prior to or during surgery, or immediately after surgery, and daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital wherein the agent is administered near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm [wherein the pharmacologic agent is administered daily in the period from immediately after surgery until symptoms of cardiovascular stress are reduced].

49. (Twice Amended) A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent [after surgery] wherein the agent is

a) administered [in the period from immediately after surgery until symptoms of cardiovascular stress are reduced] prior to or during surgery, or immediately after surgery, and daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital wherein the agent is administered near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm; [and] or

b) administered [in the period from immediately after surgery until symptoms of cardiovascular stress are reduced] prior to or during surgery, or immediately after surgery, and daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital wherein the agent is administered at about one half of the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 55 bpm, but less than 65 bpm, while the patient's systolic

blood pressure is greater than 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

50. (Amended) The method of Claim 1 in which the patient has had previous vascular surgery[, or is undergoing current vascular surgery,] or has at least two of the following cardiac risk factors: older than 65 years, hypertensive, current smoker, serum cholesterol level of at least 6.2 mmol/L, or diabetes mellitus.

Exhibit B
Claims After Entry of Amendment

1. (Three Times Amended) A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent prior to or during surgery, or immediately after surgery, and daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital wherein the agent is administered near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

2. The method of Claim 1 in which the agent is administered daily in the period after surgery until hospital discharge.

3. The method of Claim 2 in which the agent is administered daily in the period after surgery for at least three days.

4. The method of Claim 2 in which the agent is administered daily in the period after surgery for up to seven days.

5. The method of Claim 1 in which the agent is a β_1-adrenergic selective blocking agent.

6. The method of Claim 5 in which the agent is atenolol.

7. The method of Claim 1 in which the agent is an α-2 agonist.

8. The method of Claim 1 in which the agent is a nitrate.

9. The method of Claim 1 in which the agent is a calcium channel blocker.

10. The method of Claim 1 in which the agent is an ACE inhibitor.

11. The method of Claim 1 in which the agent is a platelet inhibitor.

12. The method of Claim 1 in which the agent is a thrombosis inhibitor.

13. The method of Claim 1 in which the surgery is cardiac-related surgery.

14. The method of Claim 1 in which the surgery is non-cardiac-related surgery.

15. The method of Claim 1 in which the patient suffers from coronary artery disease.

16. The method of Claim 1 wherein the patient is at risk for coronary artery disease.

49. (Twice Amended) A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent wherein the agent is

a) administered prior to or during surgery, or immediately after surgery, and daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital wherein the agent is administered near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm; or

b) administered prior to or during surgery, or immediately after surgery, and daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital wherein the agent is administered at about one half of the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 55 bpm, but less than 65 bpm, while the patient's systolic blood pressure is

greater than 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

50. The method of Claim 1 in which the patient has had previous vascular surgery or has at least two of the following cardiac risk factors: older than 65 years, hypertensive, current smoker, serum cholesterol level of at least 6.2 mmol/L, or diabetes mellitus.

51. The method of Claim 1 in which the agent is atenolol and the maximum effective dose is about 100 mg/day orally or about 10 mg BID intravenously.

52. (New) A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent prior to or during surgery, or immediately after surgery, and daily thereafter through and following hospital discharge wherein the agent is administered near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

53. (New) The method of Claim 52 wherein the agent is administered daily for six months following surgery.

54. (New) The method of Claim 52 wherein the agent is administered daily for eight months following surgery.